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Addressing current treatment challenges in Crohn's disease in real life: A physician's survey

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Abstract: **BACKGROUND:** In recent years several trials have addressed treatment challenges in Crohn's disease. Clinical trials however, represent a very special situation. **AIMS:** To perform a cross-sectional survey among gastroenterologists on the current clinical real life therapeutic approach focussing on the use of biologics. **METHODS:** A survey including six main questions on clinical management of loss of response, diagnostic evaluation prior to major treatment changes, preference for anti-tumour necrosis factor (TNF) agent, (de-)escalation strategies as well as a basic section regarding personal information was sent by mail to all gastroenterologists in Switzerland (n=318). **RESULTS:** In total, 120 questionnaires were analysed (response rate 37.7%). 90% of gastroenterologists in Switzerland use a thiopurine as the first step-up strategy (anti-TNF alone 7.5%, combination 2.5%). To address loss of response, most physicians prefer shortening the interval of anti-TNF administration followed by dose increase, switching the biologic and adding a thiopurine. In case of prolonged remission on combination therapy, the thiopurine is stopped first (52.6%) after a mean treatment duration of 15.7 months (biologic first in 41.4%). **CONCLUSIONS:** Everyday clinical practice in Crohn's disease patients appears to be incongruent with clinical data derived from major trials. Studies investigating reasons underlying these discrepancies are of need to optimize and harmonize treatment.

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Addressing current treatment challenges in Crohn's disease in real life: a physician's survey

How are current treatment paradigms in Crohn's disease patients with anti-TNF therapy addressed in real life?

TNF inhibitors use for Crohn's disease in Switzerland: a physician's survey

Stephan R. Vavricka^{1*}, Sanja Radivojevic^{1*}, Christine N. Manser², Pascal Frei³, Emanuel Burri⁴, Alain Schoepfer⁵, Laurent Peyrin-Biroulet⁶, Gerhard Rogler² and Luc Biedermann²

1 Division of Gastroenterology & Hepatology, Triemli Hospital, Zurich, Switzerland.

2 Gastroenterology & Hepatology, University Hospital Zurich, Zurich, Switzerland.

3 Division of Gastroenterology & Hepatology, Seespital Horgen, Horgen, Switzerland.

4 Division of Gastroenterology & Hepatology, Medical University Hospital Liestal, Liestal, Switzerland.

5 Division of Gastroenterology & Hepatology, University Hospital Lausanne, Lausanne, Switzerland.

6 Inserm U954 and Department of Hepato-Gastroenterology, University Hospital of Nancy-Brabois, Vandoeuvre-lès-Nancy, France.

*SRV and SR contributed equally to this work.

Correspondence: Dr. Luc Biedermann, MD; Division of Gastroenterology and Hepatology, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland. Phone: +41-(0)44-255-9334, Fax: +41-(0)44-255-9497, E-mail: luc.biedermann@usz.ch

Abstract

Background

In recent years several trials have addressed treatment-optimization, loss of response (LOR), preventing toxicity as well as over- and under-treatment with respect to immunosuppression and anti-TNF targeted therapy in Crohn's disease (CD). While the evidence available has been summarized in respective guidelines several questions with respect to the optimal time point of treatment start, efficacy of combination therapy, optimization of dosing and safety remains to be answered. Most data have been derived from clinical trials which represent a very special situation. In contrast little is known about the current real life approach in clinical practice. Therefore, we performed a cross-sectional survey.

Methods

A questionnaire including six questions was sent by mail to all gastroenterologists in Switzerland (n=318). Responses were analyzed both as a total and stratified according to pre-specified subgroups (number of IBD patients seen and treated with anti-TNF per year, years in clinical practice and practice setting).

Results

A total of 120 physicians (37.7%) responded to the survey and could be analyzed. Ninety percent of gastroenterologists in Switzerland use a thiopurine as the first step up strategy, followed by anti-TNF alone (7.5%) or in combination therapy (2.5%). The most preferred TNF-antagonist is infliximab (IFX, 47.1%) followed by adalimumab (ADA, 10.9%) and certolizumab pegol (CTZ, 0.8%), while 41.2% of all gastroenterologists have no specific preference for a TNF-antagonist. IFX is mainly preferred by gastroenterologists treating ≤ 10 patients per year with anti-TNF (57.6% vs. 35.2% for physicians treating > 10 patients per year; $p=0.02$). To address LOR most physicians prefer shortening the interval of anti-TNF administration followed by dose increase, switching the TNF-inhibitor and adding a thiopurine. In case of prolonged remission on combo therapy the thiopurine is stopped first in 52.6% of cases after a mean treatment duration of 15.7 months (TNF-inhibitor stopped first in 41.4%; both therapies continued in 4.3%; both stopped at the same time in 1.7%).

Conclusions

Everyday clinical practice significantly differs from current CD treatment paradigms.

Introduction

The introduction of tumor-necrosis factor (TNF) inhibitors more than 10 years ago in the treatment of Crohn's disease (CD) represents a major therapeutic breakthrough ¹. Since the first double-blind, placebo-controlled trial with Infliximab (IFX) ² numerous pivotal trials on the efficacy of IFX, Adalimumab (ADA) and Certolizumab pegol (CTZ) in inducing and maintaining clinical response and remission and achieving mucosal healing have been published ²⁻⁷.

Since the early days, concerns regarding safety, above all opportunistic and severe infectious as well as neoplastic diseases have been raised ^{2,8}. Even after extensive world-wide experience with anti-TNF-therapy in IBD and other indications, such as rheumatological or dermatological diseases, there still is some uncertainty about potential risks ⁹⁻¹³. In the last few years, there has been an increasing trend towards an earlier introduction of TNF-inhibitors (which is associated with a better efficacy ¹⁴) either via a rapid step up ^{15,16} or top down ¹⁷, to avoid prolonged steroid exposure and minimizing CD-associated morbidity and the need for surgery.

Since the SONIC-trial ¹⁸ the initial use of anti-TNF in combination with a thiopurine has been advocated at least in patients with high-risk features for a disabling disease course and consecutively has also been included in therapeutic guidelines ¹⁹.

Aside from treatment optimization de-escalation of therapy after variable duration of clinical remission and associated factors predicting success have been studied ²⁰⁻²². However, attitude may differ between physicians and between countries.

Also, the question of applying the best clinical strategy when confronted with loss of response (LOR) in patients receiving maintenance anti-TNF therapy has emerged. LOR occurs in a significant fraction of patients and has been reported to occur in about 20-50% of patients within the first year of therapy ^{5,23}. Switching anti-TNF has been shown to be an effective strategy in case of LOR and drug intolerance ²⁴⁻²⁷ but should be omitted simply for the reason of a more convenient route of drug administration ²⁸. Even after failure of two anti-TNF agents, there may be considerable rates of response and remission using a third one ²⁹. Nonetheless, at this point in time only in the US and Switzerland such a third agent is available without a specific reimbursement application.

The few studies having looked at adherence to guidelines among gastroenterologists have revealed equivocal results ^{30,31}. However, the treatment of CD appeared to be appropriate in most patients according to cohort studies from Switzerland and Europe ^{32,33}.

Despite a multitude of published trials clinical real life differs – looking at a selection of pivotal IBD trials, less than a third of unselected real life IBD patients would have been actually suited for

inclusion ³⁴. We thus aimed to obtain a comprehensive overview on the clinical practice of GI specialists in Switzerland involved in the care of CD patients in the biologics era and gain insights on how these challenging treatment paradigms are currently addressed in a real-life setting.

Material and Methods

A questionnaire was sent to all Swiss gastroenterologist (n = 318) by conventional mail. This questionnaire had six questions addressing step-up and de-escalation strategies in the treatment of CD and preference for any specific TNF antagonist and included also a basic section regarding personal information of the respondent (Supplementary Figure 2).

Responses were analyzed both in total as well as stratified according to the number of IBD patients seen and treated with anti-TNF per year, years in clinical practice and practice setting. Statistical Analyses were performed with SPSS (Version 21; IBM, Armonk, NY, USA) and Prism (Version 6, GraphPad Software, La Jolla, CA, USA). To investigate potential differences between the pre-specified subgroups Chi-Square testing was used.

As far as the interval on prolonged remission prior to stopping one or both medical treatments D'Agostino & Pearson omnibus normality test was used, revealing a non-normal distribution. Consecutively Kruskal-Wallis test was used to evaluate whether there are any differences in mean values between the subgroups. Mann-Whitney test was then applied to directly compare between subgroups.

Results

Response rate and characteristics of responders

Of the 318 Swiss gastroenterologists receiving our invitation to participate in the survey 120 (37.7%) responded and could be analyzed. The mean age of the responding GI specialists was 48.4 (\pm 9.8) years (89.1% male) with a mean professional experience as a gastroenterologist of 15.1 (\pm 9.3) years. The majority of gastroenterologists provide clinical care in private practice or smaller hospitals, while only about a third of responders practice in university hospitals or large non-university hospitals (Table 1).

Table 1

Number of IBD patients seen (past year)			1-30	31-100	>100		
			61 (50.8%)	44 (36.7%)	15 (12.5%)		
Number of IBD patients treated with anti-TNF (past year)			1-10	11-30	31-100	>100	
			66 (55%)	39 (32.5%)	12 (10%)	3 (2.5%)	
Practice setting* (Total)			Private practice	District hospital	Private hospital	Large non-university hospital	University hospital
			47 (38.8%)	26 (21.7%)	6.5 (5.4%)	17.5 (14.6%)	24 (19.6%)
	Practice setting* - per IBD patients seen	1-30	19.5 (32%)	16.5 (27%)	3.5 (5.7%)	10.5 (17.2%)	11 (18%)
		31-100	22.5 (51.1%)	8.5 (19.3%)	3 (6.8%)	4 (9.1%)	6 (13.6%)
		>100	4.5 (30%)	1 (6.7%)	0	3 (20%)	6.5 (43.3%)
	Practice setting* - per patients treated with anti-TNF	1-10	28.5 (43.2%)	16.5 (25%)	3.5 (5.3%)	7.5 (11.4%)	10 (15.2%)
		11-30	14.5 (37.2%)	8.5 (21.8%)	3(7.7%)	6 (15.4%)	7 (17.9%)
		31-100	2 (16.7%)	1 (8.3)	0	4 (33.3%)	5 (14.7%)
		>100	1.5 (50%)	0	0	0	1.5 (50%)

Table 1.: Baseline characteristics of responding gastroenterologists. In the lower part of the table practice setting is further stratified by IBD patients seen or IBD patients treated with anti-TNF per year, respectively (*uneven numbers are due to the fact that regarding practice setting more than one affiliation could be stated).

Preferred step up strategy?

After lack of response to systemic steroids, budesonide, 5-aminosalicylates or an inability to taper these agents, the majority of Swiss gastroenterologists (90%) use a conventional step up strategy with thiopurine as a first-line therapy. Only 7.5% of responders use anti-TNF therapy alone, 2.5% use combination therapy (thiopurine combined with TNF-inhibitor) as a first-line therapy. We did not observe any statistical differences in the strategy with regard to any of the pre-specified subgroups (number of IBD patients seen and treated with anti-TNF per year, years in clinical practice and practice setting). Notably, there is not an increased primary use of anti-TNF (either as mono-therapy or in combination with thiopurine) in referral centers versus smaller hospitals or private practise (Supplementary Figure 1).

Based on the data from the SONIC trial we calculated the efficacy of the treatment strategies according to the practicing physicians from our survey as well as the efficacy gap, assuming that in the comparison group all patients would have been receiving a combo-therapy in 1000 imaginary CD patients (Figure 1).

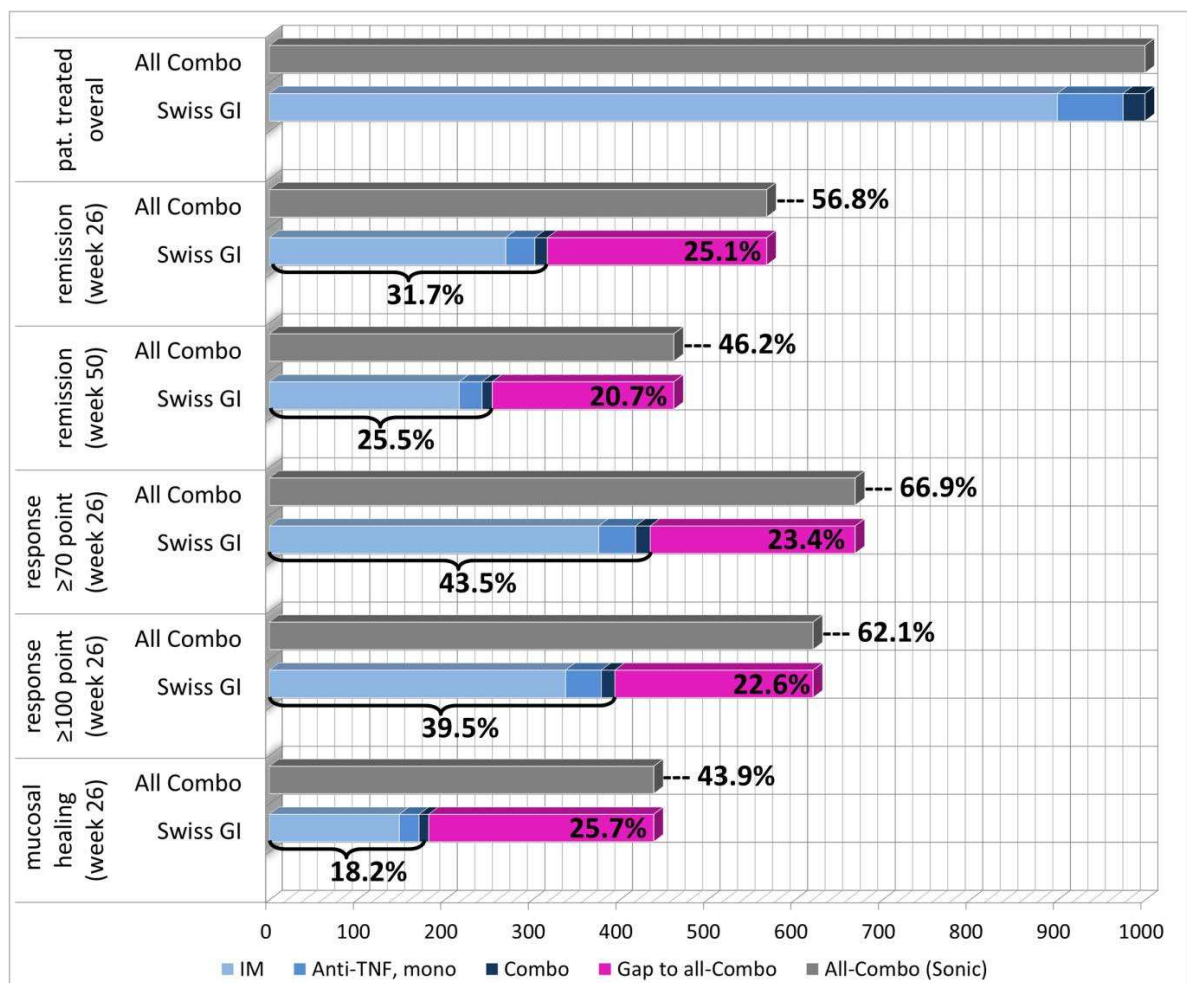


Figure 1: Preferred step-up strategy. Efficacy of an imaginary 1000 CD patients treated with the conventional approach of gastroenterologist in our survey (percentage under the brace) in comparison to the same patients treated all with combination therapy (percentage aside grey bar) is shown, including the efficacy gap (percentage within purple bar), using the established efficacy data on several endpoints from SONIC.

Preference for a specific TNF-inhibitor?

Almost half (41.2%) of Swiss gastroenterologists have no preference for a specific anti-TNF agent. Among responders having a preference for a given anti-TNF, IFX is by far the preferred anti-TNF agent (47.1%), while 10.9% and 0.8% stated ADA and CTZ, respectively, to be their initial agent of choice (Figure 2). IFX is significantly more preferred in those physicians seeing less than 30 IBD patients per year (57.4% vs. > 30 Pat: 37.3%; $p=0.03$) and those treating less or equal than 10 patients with anti-TNF per year (57.6% vs. >10 Pat: 35.2%; $p=0.02$). The preference according to the pre-specified subgroups is shown in Supplementary Figure 2.

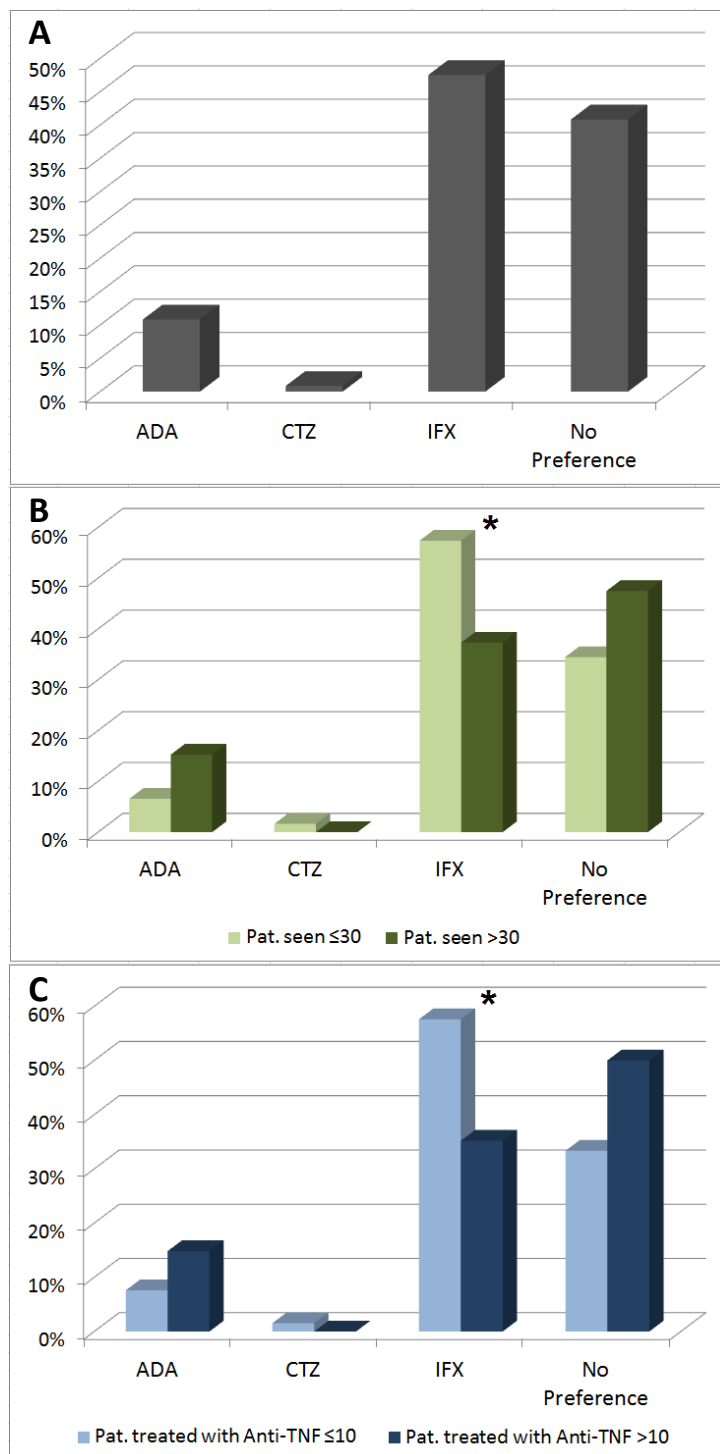


Figure 2 A, B, C: Preference for anti-TNF. The preferred agents in total (A) and per subgroups patients seen per year (B) and patients treated with anti-TNF per year (C) are depicted (significant differences between the subgroups are highlighted with asterisks; $p=0.021$ (B), $p=0.015$ (C)).

How to address loss of response?

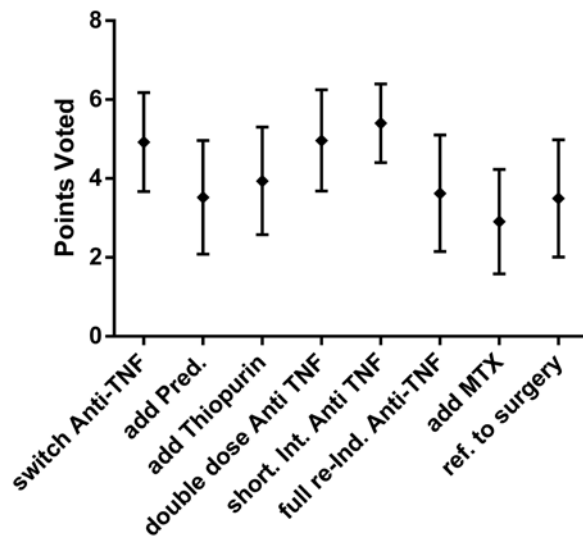
In case of LOR, the most preferred strategy is shortening the interval of anti-TNF administration.

In the questionnaire two almost identical questions aimed at investigating the preferred treatment approaches when facing LOR. However, in the first question the preferred sequence of all given treatment strategies to address LOR had to be stated (from 1 to 7 for most preferred to least preferred, respectively), while in the second question responders were to rate all given strategies on a scale from 1 to 6 (with lowest and highest agreement, respectively). As regards the separate evaluation of every provided strategy (*question II*) Swiss gastroenterologists favor three options to optimize treatment by modifying the application of anti-TNF to a similar extent: shortening the interval (mean value of all answers from the scale from 1 to 6: 5.4), increasing by doubling the dose (5.0) and switching to another anti-TNF (4.9). Adding a thiopurine (3.9), initiating a full anti-TNF re-induction (3.6), adding corticosteroids (3.5) or referring the patient to surgery (3.5) is considered inferior. Adding methotrexate (2.9) is not among the preferred strategies (Figure 3A).

However, looking at the preferred sequence of all these given strategies to address LOR (*question I*) a clearer preference of shortening the interval becomes evident: this strategy is voted as best option by the vast majority of gastroenterologists (46.9%). Doubling the dose (20.4%) and switching the TNF-inhibitor (4.4%) are less often referred to as being the best approach. The latter receives even less approval as best option than starting a full re-induction of anti-TNF (5.3%) or adding prednisone (4.4%).

We did not find any significant differences in the preference of the step-up strategy according to IBD patients seen or treated with anti-TNF per year, practice setting (hospital vs. general practice) as well as years of clinical experience.

3A



3B

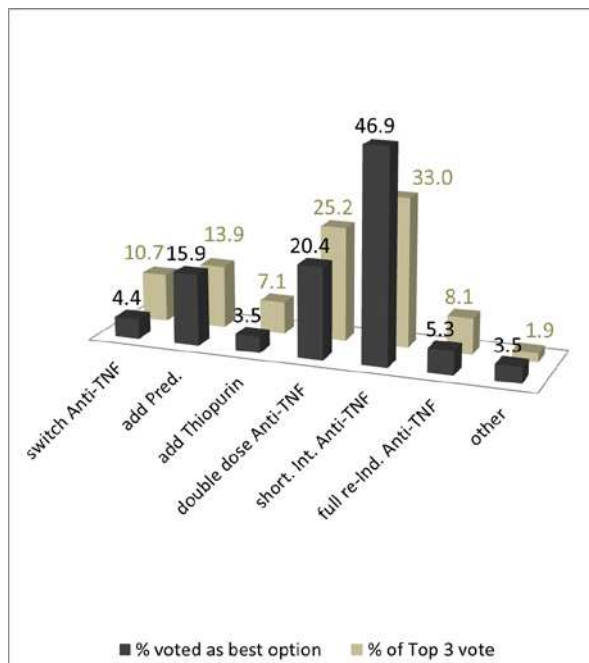


Figure 3 A, B: Preferred strategies to address LOR. Results of separate evaluation of any of the given strategies on a scale from 1-6 are depicted with error bars depicting standard deviation in Figure 3A. In Figure 3B results of sequential voting for any given option from 1 to 7 are shown. Dark bars show the percentage of any given option receiving vote as best option (1 in sequential voting), while brighter bars indicate percentage of any given option receiving a top 3 vote (1, 2 or 3 in sequential voting). In the few cases, where an individual approach was written by the respondent within the

option “other”, the most stated answers were “investigate other causes of clinical deterioration”, above all “rule out infectious cause”, “discuss surgery” and “increase dose (but not double)”.

Prolonged remission on combo therapy – how to de-escalate, and when?

In case of prolonged remission on combination therapy the gastroenterologists stop the thiopurine first in most cases (52.6%). In contrast, 41.4% prefer to primarily stop the TNF-inhibitor. Only 4.3% continue both therapies indefinitely despite prolonged remission on combination therapy, while only 1.7% of responders stop both medications at the same time (Figure 4 A). The mean interval on prolonged remission considered adequate for treatment de-escalation is 15.7 month, with a wide range from 6 to 48 month.

As far as the interval of prolonged remission with combo-therapy considered sufficient, substantial heterogeneity is observed among physicians stopping either one or both drugs (Figure 4 B). There is no significant difference in the preference for a de-escalation treatment strategy in the pre-specified subgroups. However, the interval on combo-therapy considered sufficient prior to de-escalation is significantly longer in those physicians seeing less than 30 IBD patients per year (mean 17.5 vs. 13.5 month, $p = 0.017$) and treating less than 10 IBD patients with anti-TNF, respectively (mean 17.4 vs. 13.2 month, $p < 0.01$). In contrast, no significant differences regarding the interval are observed according to hospital setting or years in practice. However, with regard to the latter, there is a trend towards a shorter interval in physicians < 10 years in practice (14.4 vs. 17.4 years in those > 10 years of professional experience, $p = 0.067$). Of note, although not significant, physicians who de-escalate within a year after initiation of treatment by trend have a stronger preference to stop the immunosuppressant first, while this is more balanced in the group de-escalating after 1 year of combo-therapy with even a trend towards stopping the TNF-inhibitor first ($p = 0.08$).

Figure 4.

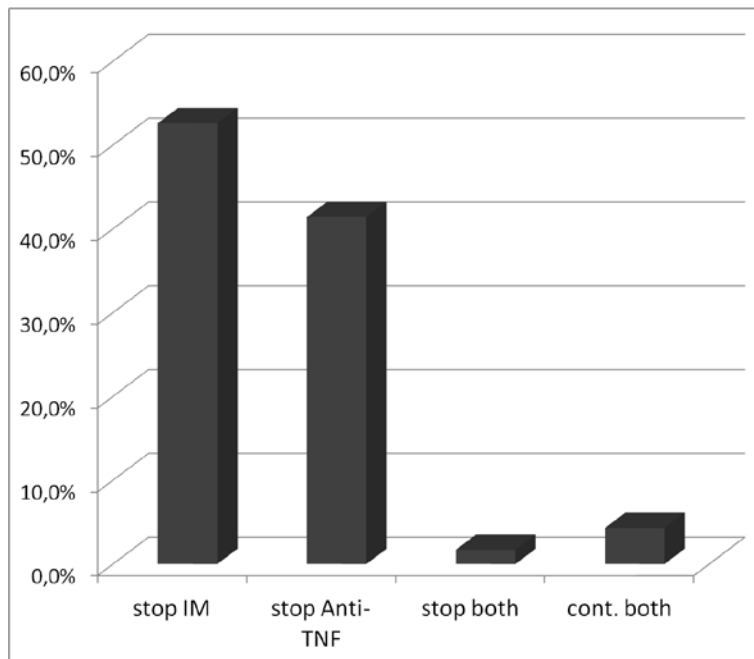


Figure 4 A

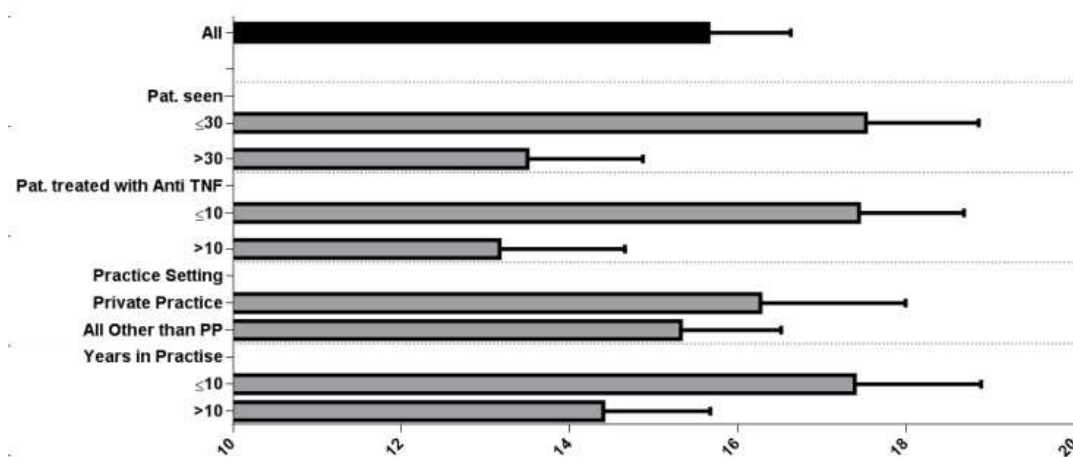


Figure 4 B

Figure 4: Treatment de-escalation. Vote for the different strategies of de-escalation are shown in Figure 4 A. The interval on remission in month (x-axis) considered adequate prior to de-escalation is shown according to physicians' subgroups (mean values with standard error mean, SEM) is depicted in Figure 4 B.

Discussion

We here report the results of a questionnaire including 6 sections regarding important treatment paradigms in CD. Despite first pivotal clinical trials addressing elements covered in this survey, a common ground of all contained issues is a lack of sufficient evidence to define the optimal clinical strategy at the present time. Yet, even if there was more evidence, the obvious differences of real-life medicine and ideal world of clinical trials ³⁴ raises concerns regarding general transferability for the clinician. Therefore, not only data on how specific treatment challenges in CD SHOULD be addressed based on clinical trials but also on how these challenges in fact ARE addressed in real life are essential to identify future needs and treatment gaps to set the stage towards an optimization in the treatment of IBD.

The preference for an immunosuppressant as the first-line step-up-option is striking, with 9 out of 10 Swiss gastroenterologist voting for this approach. However, this question did not contain any patient characteristics and one may speculate, that the answer would have differed substantially, if any indicators of a disabling disease course would have been given. Moreover, the answer does not allow drawing any conclusion, on when the treating physician would go for a next step in case of providing suboptimal clinical, biochemical or endoscopic response. The magnitude of the preference for a conventional step-up approach is nonetheless striking - especially considering the liberal reimbursement situation in Switzerland - and may appear somewhat “outdated”. However, using an immunosuppressant agent first with or without a corticosteroid is completely in line with major CD-treatment recommendations and guidelines ^{15,19,35}. This practice is not in contradiction to the increasing body of evidence, that anti-TNF based strategies are more effective in achieving crucial CD endpoints ¹⁸ and the recently published data on thiopurines, revealing no benefit of an early introduction regarding the primary endpoints ^{16,36}. Although the top-down approach has been shown to be superior in inducing remission, reducing the need for steroids and achieving mucosal healing, there was no clinical benefit regarding long-term remission rates beyond 52 weeks between early combined immunosuppression (top-down) and conventional management (bottom-up) groups ¹⁷.

Those physicians having more experience in the treatment of IBD patients clearly reveal to have less preference for a specific anti-TNF agent in general and for IFX in specific. Interestingly – in contrast to what one might assume based on the difference in the application mode between IFX and ADA/CTZ – the preference for the i.v. agent is even stronger in physicians in private practice compared to their colleagues in a hospital setting. This holds true despite the fact, that potential obstacles associated to

IFX, such as the need for an infusion unit with monitoring for potential infusion reactions and fixed treatment schedules, evidently are more of an issue in private practice.

Regarding the preferred treatment options to address LOR there apparently is somewhat a discrepancy between the answers for *question I*, where physicians were asked to provide their preferred sequence of all given options, and for *question II*, where each option was to rate independently. Sequencing the order of preferred options more clearly emerges the preference of shortening the interval. This choice is in line with current treatment recommendations to optimize treatment in LOR ^{37–40}. However, the independent rating for every option given (*question II*) is indicative of an overuse of switching the TNF-inhibitor by GI specialist participating in this survey. Adding prednisone is among the least preferred strategies in question II (3.6). Nevertheless, adding prednisone is voted as the third best option in the sequential vote, being even the most preferred strategy in one out of six gastroenterologists (15.9%). This is remarkable, as adding corticosteroids in LOR has not been shown to be effective in this setting, thus it is not included in treatment recommendations ²³. On the other hand, a watchful waiting approach in LOR patients with mild symptoms has been recommended ^{23,41}, as the symptoms of LOR may be transient without any further change of clinical management. Thus, the short-term addition of steroids indeed may be considered an adequate symptomatic bridge. Adding a thiopurine clearly is not among the preferred strategies, chosen as first option by only 3.5%.

In case of prolonged remission only a notably small fraction of gastroenterologists prefer to continue both therapies for an indefinite period of time. The vast majority performs a de-escalation of medical treatment, which may be considered in line with the current evidence from the literature, despite a growing advocacy to “never stop combo-therapy” especially in North America ⁴². In one of the very few trials prospectively investigating treatment de-escalation in CD, patients received combination treatment for a minimum of one year with a minimum of 6 month of corticosteroid-free remission. Relapse risk was strongly related to the number of several specified risk factors present ²⁰. However, in contrast to this trial the majority of gastroenterologists in our survey stop the immunosuppressive agent first, in line with another European study ²¹. Of note, those physicians seeing and treating more IBD patients per year consider a shorter interval being sufficient to initiate withdrawal of medical treatment. The wide range of this interval is in line with the current unequivocal body of evidence from the literature. The six month interval on the lower range is in line with the results from a Belgium withdrawal trial ²¹, whereas a longer interval (up to 4 years in our survey) is rather in line with a retrospective analysis ²², suggesting an increased risk of mono-therapy failure if the thiopurine is withdrawn after <27 month of combo-therapy. Currently, several questions regarding combination therapy remain unanswered, including sustained efficacy and risks beyond one year or adaptability of

the conclusions drawn from SONIC to the subcutaneous TNF-antagonists (with the current literature available, the latter may be called into question ^{43,44}). Thus, larger trials on different de-escalation strategies are an unmet need.

As with all surveys, this study has several limitations. Results from a questionnaire have always to be interpreted with caution, as a genuine image of reality cannot necessarily be presumed: Answering a questionnaire is not equal to clinical practise. The response rate of 38% may appear low. However, the rate is in line respectively rather above the typical response rates from survey studies in physicians ^{45–48}, known to be notoriously lower than in patient surveys ⁴⁸. More importantly, we believe in accurate representativity of our sample: Our results do not reflect the current clinical procedural standard from a selection of clinical opinion leaders from IBD referral centers but were obtained to a high extent from gastroenterologist in private practice. Switzerland is an ideal country to obtain this empiric data, due to the small size of the country and the limited number of GI specialists in active clinical practice, allowing the acquisition of an image representative for the whole country.

Moreover, in this country there is a substantial clinical experience with three anti-TNF agents registered for CD (apart from the US the only country in the world), including a relatively liberal reimbursement policy. The latter enables gastroenterologists in Switzerland to virtually always introduce anti-TNF in CD if considered clinically indicated which is why our results are not to be interpreted to be derived by substantial economic pressure.

Unfortunately, based on this survey, we are not able to draw any conclusions regarding the underlying reasons for differences in the preference for a specific agent (such as higher and longer experience with infliximab including the amount of available data, subjective perception of different clinical effectiveness, desire to regularly follow the patient within the fixed infusion interval, or simply monetary considerations).

To sum up, the vast majority of all Swiss GI specialists still apply a conventional step-up approach. Among those Swiss gastroenterologists having a specific preference for a TNF-inhibitor (58.2%), IFX is by far the most commonly stated agent. In case of LOR dose intensification prior to switching of the TNF-inhibitors is the most frequently used strategy. If prolonged remission has been achieved, stopping the immunosuppressant first is preferred. Although there is a large heterogeneity in what is considered an adequate interval of remission prior to de-escalation, those GI-specialist seeing more

IBD patients and using more anti-TNF therapy are applying de-escalation within a significantly shorter interval of remission. In conclusion, we here present a comprehensive overview on the clinical practice of GI specialists in Switzerland regarding common and yet insufficiently resolved treatment paradigms in CD, aiming to capture the current pace of clinical reasoning and decision-making in the care of CD patients. Our results indicate that there is a discrepancy between real-life clinical practice and implications derived from recent pivotal studies, such as the SONIC-, STORI- or “Top Down-Trial”.

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